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World J Gastroenterol 2002;8(3):406-412
World Journal of Gastroenterology
 ISSN 1007-9327

• REVIEW •

Influencing factors of pancreatic microcirculatory impairment in acute panceatitis

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Received 2001-11-02 **Accepted** 2001-12-05

Abstract

Pancreatic microcirculatory disturbance plays an important role in the pathogenesis of acute pancreatitis, and it involves a series of changes includ ing vasoconstriction, ischaemia, increased vascular permeability, impairment of nutritive tissue perfusion, ischaemia/reperfusion, leukocyte adherence, hemorrhe ological changes and impaired lymphatic drainage. Ischaemia possibly acts as an initiating factor of pancreatic microcirculatory injury in acute pa ncreatitis, or as an aggravating/continuing mechanism. The end-artery feature o f the intralobular arterioles suggests that the pancreatic microcirculation is h ighly susceptible to ischaemia. Various vasoactive mediators, as bradykinin, pla telet activating factor, endothelin and nitric oxide participate in the developm ent of microcirculatory failure.

Zhou ZG, Chen YD. Influencing factors of pancreatic microcirculatory impairment in acute panceatitis. *World J Gastroenterol* 2002;8(3):406-412

INTRODUCTION

Acute pancreatitis remains an important surgical problem with high morbidity and mortality[1-4]. It is not merely an injury caused by the activated pan creatic enzymes but also involves pancreatic ischaemia. Evidences in basic and clinical research suggest that disturbance of pancreatic microcirculation plays an important role in its pathophysiological processes[5-14]. The specific local microcirculatory changes cannot be prevented merely by adequate fluid therapy. In recent years, studies with modern molecular biological tools have elucidated that many factors are involved in the development of pancreatic microcirculatory disturbance. Whether the disturbance of pancreatic microcirculati on is an initiating factor or as a consequence of progressive pancreatitis is still debatable. The pathophysiological changes of pancreatic microcirculatory disturbance in acute pancreatitis are complex, they include local release of acina renzymes[15-25], vasoactive mediators[26-39], vasoconstriction, increase in vascular permeability, ischaemia[40-41], ischaemia/reper fusion, leukocyte adherence, intravascular coagulation, capillary stasis, etc., resulting in pancreatic oedema, hemoconcentration, and impaired capillary and ve nous drainage[42-44], consequently leading to hemorrhagic pancreatic ne crosis[45].

ROLES OF ISCHAEMIA IN PANCREATIC MICROCIRCULATORY DISTURBAN CE DURING ACUTE PANCREATITIS

Ischaemia as an initiating factor

There is a considerable evidence supporting ischaemia as an initiating factor of pancreatic microcirculatory injury in acute pancreatitis[46-48]. As long ago as 1862, Panum induced hemorrhagic pancreatitis by injection of wax droplets into pancreatic arteries. Later similar changes were noticed by intra-arter ial injection of 8-20μm microspheres, irreversibly obstructing terminal arte rioles and occluding the capillaries. While the use of larger particles only results in pancreatic oedema, because there are abundant arcade-like anastomoses between the pancreatic interlobular vessels. There is also evidence suggesting that microvascular injection of microspheres may progress to chronic active pancre atitis.

A clinical report revealed at autopsy that atheromatous thrombi embolized from the aorta into the pancreatic arteries were associated with acute pancreatitis in 10 of 12 cases. The incidence of pancreatitis in 182 patients died after cardiac surgery was 16%. There was also evidence for a high susceptibility of the pancreas to ischaemic injury in patients died of shock. A high incidence of acute pancreatitis shown after cardiopulmonary bypass operations seemed to be associated with intraoperative hypoperfusion in the splanchnic area.

By means of intravital microscopy in conjunction with technique of selected cells-labeling, direct impairments of pancreatic microcirculation in the early phase of acute pancreatitis have been observed in the experimental ischaemia induced by controlled haemorrhage or interruption of arterial blood supply to the pancreas [49], suggesting the pancreatic microcirculation being highly suscept ible to ischaemia. This is closely related to the microvasculature of pancreatic lobule; there is a single centrally-located intralobular artery as the exclusive vascular supply of each lobule, no anastomosis between the intralobular arter ies and their branches exists, indicating the cause of its high susceptibility to ischaemia[50,51].

Ischaemia as an aggravating and continuing mechanism

Temporary complete or partial ischaemia of pancreas would not cause hemorrhagic pancreatic necrosis, the slight histological and functional changes are completely reversible. However, temporary ischaemia has the potential of being transitio nal from edematous to necrotizing pancreatitis[52]. While temporary arte rial occlusion alone does not injure the pancreas following induction of edemato us pancreatitis by duct ligation[53] with hyperstimulation, arterial occ lusion for only 15 min can result in parenchymal necrosis, suggesting that isch aemia as an aggravating factor participates in the development of acute pancreat itis.

Impairment of microcirculatory perfusion of pancreas is the consequence of the effect of various local factors, such as vasoconstriction, free radicals, intravascular coagulation, release of vasoactive mediators taking part in the whole cou rse of acute pancreatitis (see below). Recently, ischaemia/reperfusion is consid ered one of the important causative factors for development of acute pancreatiti s after pancreatic transplantation. It has been repeatedly demonstrated that cha nge of pancreatic perfusion is an early event in experimental acute pancreatitis, and microcirculatory impairment in human pancreas also correlate well with the degree of ischaemic injury. These findings support the hypothesis that the micr ovasculature is the primary target of reperfusional injury after ischaemia.

CHANGES OF PANCREATIC MICROCIRCULATION IN ACUTE PANCREATITIS

Many indirect methods have been applied to assess the changes of panc reatic microcirculation during acute pancreatitis in previous studies[54]. Recently, intravital fluorescence microscopy combined with the technique of separate labeled-cells and computerized image analysis system has been successf ully used in the studies of pancreatic microcirculation in acute pancreatitis. Many important phenomena as vascular permeability change, vasoconstriction, capil lary blood flow, functional capillary density, leukocyte-endothelium int eraction, etc., have been continuously and directly observed during the course of acute pancreatitis. It is now believed that microcirculatory changes is import ant as well as early feature in the pathophysiology of acute pancreatitis[55].

Vasoconstriction

The first step in the sequence of microcirculatory events in pancreatitis is the constriction of interlobular vessels, especially in the proximal segments of the interlobular arterioles and venules[56,57]. The vasoconstriction occu rring in the early phase of acute pancreatitis may cause ischaemia and stasis of the microcirculation[58], which can be prevented by the radical scaveng ers, superoxide dismutase and N- (2-mercaptopropionyl)glycine in sodium tauroc holate-induced pancreatitis, suggesting that vasoconstriction might be induced by free radicals. There is also great support for the concept that solutions inj ected into the pancreatic duct to induce biliary pancreatitis exert their effect via the interstitial route. Even at a low injection pressure of 40 cmH_2O, ru pture of the ducto-acinar junction is detectable with subsequent fluid extravas ation in the interstitial space, where they gain access to the pancreatic microv asculature precipitating vascular spasm. It has been noticed that segmental cons triction of pancreatic arteries occured in bile-induced pancreatitis, and of me senteric arteries directly exposed to diluted bile. There is also pronounced dam age to the pancreatic vessels resulting in haemorrhage, endothelial detachment and thrombosis, as has been shown with the taurocholate, trypsin, and trypsin-di gested blood vessels. The vasotoxic effect of these substances was further subst antiated by the demonstration that interstitial injection into the omentum preci pitates similar changes at the injection site. The finding that stress and shock can convert oedematous to hemorrhagic experimental pancreatitis suggests that catecholamines mediators might participate in the process. Therefore, pancreatic vasoconstriction in acute pancreatitis might be relevant to a variety of factors.

Changes of permeability

The intravital microscopic findings of immediate leakage of the macromolecular plasma marker (FITC-Dextran 70) from the microvasculature into the interstitial tissue, and the scanning electron microscopic evidence of leakage of the cast ma terial through the capillary membrane in the early phase of acute experimental pancreatitis suggest that presence of increased permeability during the disease process. Further experiments demonstrate that permeability changes precede stasis and stasis precedes leukocyte adherence[59], suggesting that increased vascular permeability and ischaemia are the initial microcirculatory lesions in acute pancreatitis induced by sodium taurocholate leading to haemorrhagic necrosis. The non-specific detergent effect of sodium taurocholate and bile acids in general seems to be responsible for the initial changes due to the direct dissol ution of cellular membranes.

Changes of nutritive tissue perfusion

Acute pancreatitis is characterized by impairment of nutritive tissue perfusion as a consequence of gradually decreased capillary blood flow and functional capi llary density[60]. Reduction of capillary infusion volume and of functio nal capillary density has been observed with intravital microscopy and laser-Doppler flowmetry in the experiments of acute pancreatitis. In such experiments, capillaries are progressively excluded from perfusion starting 30min after the induction of pancreatitis, and with only few capillaries remaining perfused after 3h. At the same time, flow through the preferential pathways is maintained. Measurements of pancreatic blood flow during acute pancreatitis have ever yielded conflicting results. Some found no change or even increased blood flow, but most experiments have repeatedly demonstrated decreased total blood flow in acute pancreatitis. The perfusion values with an initial increase followed by a sharp decrease have been observed. Increased pancreatic blood flow is considered as a consequence of vasodilatation in acute inflammation. Because of the tremendousd istributional disturbances of the microcirculation in the pancreas, however, mea surements of total blood flow of the pancreatitis do not reflect proportionately the pathological status of different local regional perfusion within the pancre as. The pathological states, both the hyperemia and ischaemia, can be found at the same time in the different regions within the pancreas, thus emphasizing the importance of capillary blood flow measurement for accurate evaluation of microc irculatory blood flow changes. In most of the studies the degree of pancreatic h ypoperfusion was found to be disproportionately more severe than the decrease in cardiac output at comparable intervals. Moreover it has been shown that a decre ase in pancreatic perfusion cannot be prevented by adequate fluid therapy using Ringer's solution even though cardiovascular parameters are stabilized at the ba seline level, proposing a specific mechanism of local microcirculatory ischaemic impairment[61-63].

Impairment of ischaemia/reperfusion and leukocyte adherence

Ischaemia/reperfusion of the pancreas with impairment of the microcirculation has attracted attention both in experimental and clinical studies of acute pancrea titis[64-73]. Ischaemia/reperfusion leads to the adherence of leukocytes to the vascular endothelium. In parallel with reduction of functional capillary density, an increase of heterogeneity of capillary perfusion has been noted. Primary capillary perfusion failure after onset of reperfusion is a characteristi c microcirculatory feature of ischaemia and is called no-reflow phenomenon. Among various stimuli promoting leukocyte-endothelium interaction are ischaemi a/reperfusion and formation of oxygen free radicals leading to rolling and adher ence of leukocytes, the latter provoking the "reflow/paradox" phenomenon with loss of endothelial integrity and macromolecular leakage as an end result. Enhanced generation of oxygen radicals elicits ischaemia/reperfusion-induced leu kocyte infiltration in the tissue, which is instrumental in the progression of a cute pancreatitis. Degree of endothelial cell dysfunction and severity of leukocyte adherence is dependent upon the duration of ischaemia and reperfusion. Complete ischaemia/reperfusion of the pancreas induces extensive capillary stasis,i. e. pancreatic microcirculatory failure.

Effect of hemorrheological changes

Since blood viscosity is the inherent resistance of blood to flow, it is probable that the hemorrheological changes might be important to acute necrotizing panc ratitis[74-84]. 188 Wistar rats were studied by measuring hemorrheologi cal and stereological parameters of pancreatic microvasculature. The results sho wed that increased blood viscosity, causing red blood cell aggregation with roul eaux formation, and decreased erythrocyte deformability are responsible for panc reatic microcirculatory disturbances and play an important role in the transitio n of oedematous pancreatitis to necrosis.

It has been noticed that the time points in the course of

experimental acute pan creatitis are extremely variable. This can be explained as investigators with various pancreatitis models, different infused substance, concentration, volume as well as intraductal pressure, the latter may be more important than the others. The high intraductal injection pressure results in an increased leakage of bile and a more generalized distribution in the interstitial space, even immediateh emorrhagic pancreatic necrosis, thus emphasizing the pathophysiological signific ance of experimental models in acute pancreatitis. In the low-pressure ductal p erfusion model the etiological factor and the pathophysiological course are simi lar to those associated with the disease clinically.

VASOACTIVE MEDIATORS IN ACUTE PANCREATITIS

Bradykinin

Bradykinin probably exerts its influences upon microvessels via several pathways involving endothelial cells, including stimulating the formation and release of NO, arachidonic acid metabolites and tackykinins. Microcirculatory responses to bradykinin are biphasic: at low concentrations it causes vasodilatation, while at higher concentrations it causes vasoconstriction.

The role which bradykinin plays in microcirculatory impairment of acute pancreat itis is controversial. It was noticed that in sodium taurocholate-induced pancr eatitis, the number of perfused capillaries was increased and capillary flow pre served and the mean venular leukocyte adherence decreased and histopathological change improved in icatibant (a B2 receptor antagonist)-treated rats; kinase II inhibitor captopril or exogenous bradykinin in addition to an otherwise effective dosage of icatibant resulted in microcirculatory stasis, extensive venularleu kocyte adherence and severe histological damage, indicating that bradykinin may aggravate the microcirculatory disturbance[85,86]. But another study showed that B2 receptor antagonist increased the severity of acute pancreatitis, while lys-bradykinin substituting bradykinin didn't[87].

Platelet-activating factor(PAF)

PAF acts on microvasular diameter, permeability and leukocyte rolling, adhesion and migration through different mechanisms, including synthesis and release of NO and arachidonic acid metabolites, and upregulated expressions of ICAM-1 and CD11/CD18. Actions of PAF on microvasculature have the following features: constr iction response of venules to PAF is stronger than that of the arterioles; its a ction on arteriolar diameter is biphasic.

It was observed that treatment with PAF receptor antagonist improved pancreatic capillary blood flow, reduced the severity of pancreatitis-associated endothelial barrier compromise and pancreatic leukocyte recruitment, suggesting that PAF is proinflammatory in pancreatitis[88-92].

Endothelin(ET)

There are three kinds of endothelins, and endothelin-1 is predominantly expressed by vascular endothelial cells. There are three types of endothelin receptors, and ETA receptor is endothelin-1 selective, and found mainly on vascular smoot hmuscle cells, mediating vasoconstriction; ETB is nonselective and expressed by endothelial cells; it mediates vasodilatation through the release of NO and pro stacyclin. The action of endothelin-1 on microvessels is biphasic: at low conce ntration, it causes vasodilatation; at higher concentration, it causes sustained vasoconstriction.

Several experiments demonstrated that endothelin-1 was involved in the microcir culatory disturbance and in the development and progression of acute pancreatitis[93-99]. Administration of endothelin-1 after the caerulein injection decreased pancreatic blood flow significantly, aggravating microcirculatory dis turbance. Topically superfused endothelin-1 induced pancreatic microvascular de terioration and acinar cell injury similar to that induced by intraductal infusi on of sodium taurocholate in rats[100]. Studies also showed that ETA rec eptor antagonist is protective in microcirculatory disturbance of acute pancreat itis[101].

Nitric oxide (NO)

NO is formed from L-arginine by NO synthase(NOS). cNOS(constitutive form) catalyzes formation of NO of physiological level. Catalytic activity of iNOS(inducibl e form) is stronger and lasts longer than that of cNOS, and NO of higher than physiological level is produced by iNOS. NO dilates blood vessels, but at higher concentrations it is cytotoxic.

Pancreatic NO level in acute pancreatitis may be decreased[102] or signi ficantly elevated in different experiments. Intravenous administration of L-arginine to rats with hemorrhagic pancreatitis improved pancreatic blood flow and a meliorated the severity of pancreatitis in a dose-dependent manner, while nitro -L-arginine infusion to the rats with edematous pancreatitis caused a decrease in pancreatic blood flow and exacerbated pancreatitis, indicating that NO is pr otective[103-106]. However, some experiments showed that NO was not inv olved in the progression from edematous to hemorrhagic pancreatitis. Even microc irculatory changes were significantly alleviated in caerulein-induced pancreati tis pretreated with nitro-L-arginine, suggesting NO may be proinflammatory[107]; it was found that L-arginine improved the pancreatic microcirculation but worsened the microscopic alterations within the pancreas[108,109].

Adhesion molecules

Leukocyte-endothelial interaction is an important step in the development of ac ute pancreatitis. It was demonstrated by experiments that levels of ICAM-1, PEC AM-1 and ELAM-1 were upregulated, and expressions of P- and E-selectin enhanced, and leukocytes became CD18-positive in acute pancreatitis[110,111]. Immunoneutralization of adhesion molecules was proven effective in the treat ment of acute pancreatitis[112]. Administration of monoclonal antibody a gainst ICAM-1 to rats with acute severe pancreatitis significantly enhanced cap illary blood fow in the pancreas, reduced leukocyte rolling and stabilized capil lary permeability[113].

PATHOGENESIS OF MICROCIRCULATORY FAILURE IN ACUTE PANCREATITIS

The pancreatic microcirculation is impaired in acute pancreatitis[114-124]. Capillary stasis may be due to a variety of mechanisms including hemoconce ntation and intravascular coagulation, generation of oxygen free radicals in the microenviroment of the pancreatic ducto-acinar complex, increase in interstiti al pressure, increase in leukocyte-endothelium interaction[125], and local reduction of endothelial derived relaxation factor (nitrous oxide)[126]. An acinar abnormality may be the initiating factor arising from a combinat ion of ductal obstruction and exocrine hypersecretion followed by an increase in intraductal pressure and leakage of enzymes into the pancreatic interstitium with release of zymogen and lysozymes.

Hemoconcentration and intravascular coagulation play an additional role in the d evelopment of pancreatic ischaemia in acute pancreatitis. The increased capillary permeability is the initial feature of experimental biliary pancreatitis, resu lting in loss of fluid and cells into the pancreatic interstitium induced by osmolarity shifts either in the duct or extracellular fluid[127]. Local hem oconcentration takes place at the site of plasma sequestration, even if the syst emic hematocrit is maintained at the initial level. In conjunction with the impa irment of endothelium, intravascular coagulation occurs and causes a further dec rease of blood fluidity. These changes are

aggravated by a systemic hypercoagula rity in acute pancreatitis, probably due to thromboplastic material and activate d trypsin gaining access to the systemic circulation.

The mechanism of oxygen free radical is important in acute pancreatitis of any causes[128] and is a direct sequel of biliopancreatic reflux at the onset of acute biliary pancreatitis. Besides disintegration of cell membranes by lipid peroxidation, free radicals trigger the extravasation of granulocytes into the surrounding parenchyma representing an early lesion in acute experimental pancr eatitis. The initial margination of granulocytes in the capillaries may be a con tributing factor in endothelial injury and impairment of capillary perfusion. Ox ygen radicals mediate depletion of pancreatic sulphydryl compounds with changes in both lipid peroxide and oxygen radical scavengers. Serum concentrations of vi tamin C, a potent antioxidant, are depleted in acute pancreatitis so that synthe tic ascorbic acid derivatives have been used as a free radical scavenger.

Postischemic intensive adherence of leukocytes to the endothelium of the venules and adhesive leukocytes forming plaques partially occluding the lumen of the venules have been observed within the reperfusional period in the experimental acu te pancreatitis. This adhesive interaction is largely confined to postcapillary venules. And it is determined by a variety of factors such as expression of adhe sion molecules on leukocytes and/or endothelial cells, products of leukocyte (su peroxide) and endothelial cell (nitric oxide) activation and physical forces gen erated by the movement of blood along the vessel wall[129,130]. The fir m adhesion of leukocytes that take place within postcapillary venules may increases the postcapillary pressure more than 200 folds, cause the passive dilatation of the capillaries and microcirculatory stasis. Many studies show that some com pounds appear to be effective in reducing or abolishing leukocyte-endothelial cell adhesion, whereas some classical anti-inflammatory drugs such as indomethac in and aspirin actually promote leukocyte adhesion in the venules.

There may also be relation to lymphatic drainage[131]. Increase in local interstitial pressure as a consequence of obstructed lymph drainage further interferes with pancreatic microperfusion due to the venous outflow impairment. In the early period of acute experimental pancreatitis, dilated lymphatic vessels are visible macroscopically, and further progress of oedema with consequent focal hemorrhagic pancreatic necrosis is possible in case of insufficient lymphaticd rainage. Experiment demonstrates that an increase of thoracic duct lymph flow fo llowed by a pronounced and prolonged reduction. Erythrocytes originating from pa ncreatic interstitial hemorrhages were shown to enter and obstruct the microlymp hatics.

CONCLUSIONS

Recent advances in experimental research have helped witness the pathophysiology of acute pancreatitis. The phenomena of microcirculatory changes observed in ac ute experimental pancreatitis during the past few years gradually underlie the disturbance of the local microcirculation in acute pancreatitis, but several chal lenges remain. Still some questions remain unexplained concerning the mechanisms: (1)Which is the first event in the pathogenesis of acute pancreatitis? (2)Which factor determines the edematous or hemorrhagic necrotizing pancreatitis in a given experimental or clinical situation? (3)What is the role of impaired distribu tion of blood supply in early steps of acute pancreatitis? The potential vasoact ive mediators responsible for the progression of the disease severity have largely remained subjecting to speculation and debate.

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Edited by Wu XN